Congenital Lactase Deficiency (CLD) is a severe, infant-onset form of lactose intolerance that leads to diarrhea1. This disease is caused by autosomal recessive mutations in the lactase enzyme gene LCT2. There are at least nine different identified mutations, of which most are nonsense mutations3,4,5,6. Truncated LCT proteins cause obvious structural and functional problems, but it is *unknown how the single amino acid substitutions in the C-terminus disrupt lactase function during embryonic development.* Studying the evolution of LCT can also help elucidate its function and importance. Mutations in the conserved lactase activity region could affect the overall charge balance and pH and impact the structure of the folded protein and its subsequent trafficking.

The **overall objective** is to understand how the mutation R1587H (arginine to histidine substitution at 1587) affects the structure, trafficking, and substrate interaction of LCT to understand how it may hinder the enzyme function. The **central hypothesis**is that the R1587H mutation will cause significant changes in the pH and structure of LCT, which will cause decreased trafficking of the enzyme from the endoplasmic reticulum and decreased interaction of mature lactase with lactose. This study will use the model organism mouse (*M. musculus*) to study lactase function. Mouse has a homologous gene LCT which maintains the same functions as human LCT, and it is easy to observe the symptoms, so it will serve as an excellent disease for CLD.

The **long-term goal** of this study is to elucidate the mechanisms in which single amino acid changes in the C-terminus cause lactase loss of function.

**Aim 1**: Understand the evolutionary history of LCT and conservation of the C-terminus and R1587

Rationale: Understanding the evolutionary history could elucidate the importance of LCT in development. Creating phylogenetic trees based on the gene and protein could identify important evolutionary patterns and conserved regions.

Approach: Use phylogenomics approach to create phylogenetic trees to trace the evolutionary history of the gene between organisms and its conserved domains. Also specifically examine conservation of the C-terminus and the 1587 arginine.

References

[1] Genetics Home Reference (2019). Lactose Intolerance. U.S. National Library of Medicine. Retrieved from <https://ghr.nlm.nih.gov/condition/lactose-intolerance#genes>

[2] Kuokkanen, M. et. al. (2006, February). Mutations in the Translated Region of the Lactase Gene (LCT) Underlie Congenital Lactase Deficiency. American Journal on Human Genetics. Retrieved from <https://www.sciencedirect.com/science/article/pii/S0002929707623647>

[3] Torniainen, S. et al. (2009, January). Four novel mutations in the lactase gene (LCT) underlying congenital lactase deficiency (CLD). BMC Gastroenterology. Retrieved from [www.ncbi.nlm.nih.gov/pubmed/19161632](http://www.ncbi.nlm.nih.gov/pubmed/19161632)

[4] Uchida, N. et al. (2012). Two Novel Mutations in the Lactase Gene in a Japanese Infant with Congenital Lactase Deficiency. The Tohoku Journal of Experimental Medicine. Retrieved from [www.jstage.jst.go.jp/article/tjem/227/1/227\_69/\_article/-char/ja/](http://www.jstage.jst.go.jp/article/tjem/227/1/227_69/_article/-char/ja/)

[5] Diekmann, L et al. (2015, March). Congenital lactose intolerance is triggered by severe mutations on both alleles of the lactase gene. BMC Gastroenterology. Retrieved from [bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-015-0261-y](file:///C:\Users\HayBa\Documents\School\2018-19\Spring%20Semester\Genetics%20564\Aims\bmcgastroenterol.biomedcentral.com\articles\10.1186\s12876-015-0261-y)

[6] Fazeli, W. et al. (2015, May). A novel mutation within the lactase gene (LCT): the first report of congenital lactase deficiency diagnosed in Central Europe. BMC Gastroenterology. Retrieved from <https://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-015-0316-0>

[7] Behrendt, M. et al. (2009, June). Impaired Trafficking and Subcellular Localization of a Mutant Lactase Associated with Congenital Lactase Deficiency. Gastroenterology. Retrieved from <https://www.sciencedirect.com/science/article/pii/S0016508509001425>